



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification <sup>5</sup> :  A61K 31/54		A1	(11) International Publication Number: <b>WO 94/03174</b>  (43) International Publication Date: 17 February 1994 (17.02.94)
<p>(21) International Application Number: PCT/GB93/01607</p> <p>(22) International Filing Date: 29 July 1993 (29.07.93)</p> <p>(30) Priority data: 9216155.3 30 July 1992 (30.07.92) GB</p> <p>(71) Applicant <i>(for GB only)</i>: HOLMES, Michael, John [GB/GB]; Frank B. Dehn &amp; Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).</p> <p>(71) Applicant <i>(for all designated States except US)</i>: ED GEISTLICH SÖHNE AG FÜR CHEMISCHE INDUSTRIE [CH/CH]; CH-6110 Wolhusen (CH).</p> <p>(72) Inventors; and            (75) Inventors/Applicants <i>(for US only)</i> : PFIRRMANN, Rolf, Wilhelm [CH/CH]; Schadrudistrasse 27, CH-6006 Lucerne (CH). GEISTLICH, Peter [CH/CH]; Kehrsitenstrasse 19, CH-6362 Stansstad (CH).</p>		<p>(74) Common Representatives: HOLMES, Michael, John et al.; Frank B. Dehn &amp; Co., Imperial House, 15-19 Kingsway, London WC2B 6UZ (GB).</p> <p>(81) Designated States: CA, JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).</p> <p>Published <i>With international search report.</i></p>	
<p><b>(54) Title:</b> TREATMENT OF DENTOALVEOLAR INFECTIONS WITH TAUROLIDINE AND/OR TAURULTAM</p> <p><b>(57) Abstract</b></p> <p>The present invention provides a new means of combatting severe dentoalveolar infections such as dental gangrene, parodontitis and abscesses which involves the administration of the methylol-transfer agents taurolidine and/or taurultam. In one embodiment the taurolidine and/or taurultam compositions may be administered prophylactically to combat post-operative infection. Certain novel compositions comprising taurolidine and or taurultam are also described.</p>			

**FOR THE PURPOSES OF INFORMATION ONLY**

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	FR	France	MR	Mauritania
AU	Australia	GA	Gabon	MW	Malawi
BB	Barbados	GB	United Kingdom	NE	Niger
BE	Belgium	GN	Guinea	NL	Netherlands
BF	Burkina Faso	GR	Greece	NO	Norway
BG	Bulgaria	HU	Hungary	NZ	New Zealand
BJ	Benin	IE	Ireland	PL	Poland
BR	Brazil	IT	Italy	PT	Portugal
BY	Belarus	JP	Japan	RO	Romania
CA	Canada	KP	Democratic People's Republic of Korea	RU	Russian Federation
CF	Central African Republic	KR	Republic of Korea	SD	Sudan
CG	Congo	KZ	Kazakhstan	SE	Sweden
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovak Republic
CM	Cameroon	LU	Luxembourg	SN	Senegal
CN	China	LV	Latvia	TD	Chad
CS	Czechoslovakia	MC	Monaco	TG	Togo
CZ	Czech Republic	MG	Madagascar	UA	Ukraine
DE	Germany	ML	Mali	US	United States of America
DK	Denmark	MN	Mongolia	UZ	Uzbekistan
ES	Spain			VN	Viet Nam
FI	Finland				

## TREATMENT OF DENTOALVEOLAR INFECTIONS WITH TAUROLIDINE AND/OR TAURULTAM

The present invention is concerned with the combatting tooth and gum infections, in particular severe dental infections which are located within the alveolar region of the jaw.

Oral infections remain a relatively common cause of pain and discomfort to many patients and combatting such infections thus continues to be of clinical importance.

It was originally believed that the primary cause of dentoalveolar infection was a simple combination of Gram positive and Gram negative aerobic bacteria. Improvements in microbiological techniques have however now led to the realisation that such conditions are in fact usually caused by a mixed aerobic/anaerobic bacterial population, with Gram negative anaerobes playing an important part in the polymicrobial process.

The complex aetiology of oral infections results in the observation of widely variable resistance patterns following administration of conventional oral antibacterial preparations. Such preparations may also not be sufficiently active against some of the pathogenic organisms present. There is thus a need for a wide-spectrum agent to treat such mixed infections. Administration of an agent which is ineffective against some of the bacteria present will result in proliferation of the resistant bacterial species and complete elimination of the infection may not be achieved. Typically, the types of bacteria present in dentoalveolar infections include aerobes such as Streptococcus viridans gr., Streptococcus gr C., Corynebacterium spp., Neisseria spp and Haemophilus influenzae. Anaerobes which are also commonly present include Peptococcus spp., Bacteroides spp. and Furobacterium spp.

- 2 -

Conventional treatments include bactericidal agents such as chlorophenol-camphor-menthol, chlorhexidine and antibiotics such as chlortetracyclin and tetracinolon. However such agents are not without unpleasant side-effects including allergic reactions, toxic tissue reactions causing inflammation and necrosis, tooth or filling discoloration and affecting the senses of taste and smell. Moreover, conventional agents require a relatively prolonged period of treatment to be completely effective.

The use of Chlortetracycline and Democlocycline is considered inadvisable because of their instability and increased toxicity. It has been shown in this connection, that formation of the highly nephro-toxic anhydro-4-epitetracyclin-hydrochloride occurs in older Tetracycline preparations.

The aminoglycoside antibiotic Neomycin may only be applied locally because of its extreme nephrotoxic, ototoxic and muscle relaxant properties. In this context, it is to be noted that resorption can occur when the ectoderm is damaged (i.e. marginal and apical parodontitis, mucous-membrane ulceration) and repeated usage can lead to analogous side-effects. Because of multiple resistant germ strains and an allergy rate of 15-30%, the withdrawal of this preparation was suggested in 1975. The quinoline derivative Aminoquinuride (Surfen), which increases the spectrum of Neomycin, has not been investigated sufficiently and its effectiveness is controversial.

Synthetic corticosteroid derivatives like Prednisolone and Triamcinolone are intended to supercede the role of an analgesic in combination preparations. Although their strong anti-inflammatory and anti-allergic properties make for a quick reduction of pain this would always be accompanied by an immune separation which arises out of a comprehensive inhibition mesenchymal reaction. As well as an inhibition of the

- 3 -

lympho-reticular system, damage also arises to the DNA-repair and mitosis capability which can lead to tissue atrophy. The fibrinogen concentration in the plasma is reduced by simultaneously strengthened fibrinolysis. It has been shown that the slow release of the working substance due to the insolubility of glucocortoid, conceals the danger that it will exhaust the efficacy of antibiotic too soon and thereby the infection could either spread unrestrained, or develop into a chronic condition. The unpleasant taste of prednisolone has also proved a deterrent against its use.

Although Chlorophenol-Camphor and Chlorophenol-Camphor-Menthol solutions are often recommended for root canal instillation and no significantly higher or stronger pain sensation following instillation in the pulpal cavity has been reported as against comparative clinical experiments, the high toxic potential is undisputed. In animal experiments strong tissue toxic reactions have been observed in the form of inflammation and necrosis formation.

Chlorhexidine, which has proved itself in extensive experimental and clinical studies as a broad spectrum anti-microbial, is also cell damaging. In tests carried out on human desmodontal fibroblasts, accelerated ageing and a cytopathological effect were demonstrated. The release of p-chloroaniline as a possible by-product of chlorhexidine, which is suspected of causing mutation and of being carcinogenic, is often denied.

It has now been found that taurolidine is effective against oral infections, especially those that are located within the infrastructure of the jaw, but exhibits a much reduced level of side-effects and provides effective relief in a shorter period.

Additionally, administration of suitable taurolidine containing compositions will neutralise bacterially originating endo- and exo-toxins as well as attacking the bacteria themselves.

- 4 -

Taurolidine is a synthetic derivative of the naturally occurring 2-aminoethane sulphonic acid, taurine. The use of taurolidine as a potential antimicrobial substance, acting by a methylol transfer mechanism, has been disclosed in GB 1,124,285. It is sold by Ed. Geistlich Sohne AG. under the registered Trade Mark 'Taurolin'. The antibacterial substance taurultam is closely related to taurolidine and, indeed, is formed during the methylol transfer reaction between taurolidine and target substances. It is also produced by Ed. Geistlich Sohne AG. Taurultam is slightly more water soluble than taurolidine but possesses fewer methylol transfer groupings.

Taurolidine and taurultam containing toothpastes, toothgels and mouthwashes have also been disclosed in GB 1557163 and it was suggested that such formulations could be used generally in dental care, but were particularly useful in the treatment of parodontosis (a degenerative, non-inflammatory condition of the gums (periodontium) surrounding the teeth which can result in the destruction of the tissues). The treatment of alveolitis (an infection located within a tooth socket) using a taurolidine gel fine granulate has also been proposed (see Nentwig et al., "Erste klinische Erfahrung mit Taurolin-Feingranulat in der zahnärztlichen Chirurgie" in Taurolin-Ein neues Konzept zur antimikrobiellen Chemotherapie chirurgischer Infektion ed. Brückner, 1985, pages 287-289).

However, it was not previously appreciated that taurolidine compositions would be useful in combatting other, more severe dental infections such as gangrene, parodontitis and abscesses. Neither was it known that administration of a taurolidine composition was so much more effective as regards reducing the length of time and the dosage required for treatment.

Thus, the present invention provides the use of taurolidine and/or taurultam in the preparation of an

- 5 -

orally acceptable medicament for combatting severe dental infections or dental infection following dental surgery.

The term "combatting" as used herein includes both therapeutic and prophylactic treatment. The term "severe dental infections" is used herein to refer to those infections which have become established in the interior of the jaw infrastructure, eg. dentoalveolar infections, such as gangrene, parodontitis or dental abscesses.

The condition parodontitis (or periodontitis) is an inflammatory reaction of the tissues surrounding a tooth and can be characterised by formation of periodontal pockets, pus formation, bone resorption, destruction of the periodontal ligament and tooth loss. Parodontitis is a different condition from parodontosis.

One advantage of this aspect of the invention is that the long term pain (toothache) is more rapidly reduced as compared with other antibacterial treatments. This is thought to be due to direct action of the active compounds on tumour necrosis factor (TNF), which is the cytokine responsible for many pain reactions.

It has also been found that taurolidine and/or taurultam can be used prophylactically following surgery such as implantation.

Dental, mandibular or maxillofacial surgery is relatively common and varies from a complete restructuring of the jaw bone, (for example following injury to that area) to replacement of a natural tooth with an artificial dentiform implant (false tooth). Removal of a natural tooth may have occurred by accident, for example resulting from a blow to the face, or may be undertaken by surgical techniques made necessary by, for example, untreated decay of the tooth structure. Where a false tooth is to be inserted, the tooth socket is generally prepared by the dental surgeon. Usually a titanium implant is first located in the tooth socket,

- 6 -

and then the false tooth proper is firmly attached to the titanium implant, conveniently by means of opposing screw threads so that the false tooth may be simply screwed into place. However, there is a high incidence of post-operative infection which can cause the patient much pain and discomfort, but more seriously can also lead to the ultimate rejection of the implant.

Infection is a particular problem in the mouth since mixed populations of endogenous bacteria are always present and consumption of fresh food inevitably leads to the introduction of bacteria into the mouth.

Moreover it is virtually impossible to sterilise the mouth for sustained periods of time and the moist, warm conditions are ideal for bacterial reproduction.

It has however now been found that taurolidine and/or taurultam can be used prophylactically, for example by simple local application, to greatly reduce the incidence of post-operative infection.

The present invention thus provides the use of taurolidine and/or taurultam in the preparation of an orally acceptable prophylactic medicament to prevent dental or gum infections, and in particular to prevent such infections following dental, mandibular or maxillofacial surgery.

Particularly suitable compositions of taurolidine and/or taurultam which may be used to combat severe dental infections (as defined above) or as a prophylaxis include gels, emulsions, liquid gel or rinse solutions.

Certain of these compositions are new and comprise a further aspect of the present invention.

One particular formulation for use in combatting tooth infections is an aqueous emulsion comprising taurolidine or taurultam in solution in the aqueous phase. The oily phase of such an emulsion can comprise a physiologically acceptable oil eg. a food oil such as soya or arachis oil. One or more emulsifiers can be present, for example non-ionic emulsifiers such as

- 7 -

glyceryl monostearate, fatty alcohols such as cetyl or myristyl alcohol, or lecithin. A thickening agent such as hydroxyethylcellulose (Natrosol 250 HHR), carboxymethylcellulose, polyethylene glycol, sodium alginate, polyacrylic acid cross-linked by an alkyl ether of pentaerythritol or sucrose (Carbopol) or polyvinylpyrrolidone is desirably added. The advantage of such a formulation is delayed release of the taurolidine or taurultam when the formulation is introduced in the vicinity of the infection and resistance to elimination from the site of infection by saliva.

Accordingly, the present invention further provides an orally acceptable composition, said composition comprising taurolidine and/or taurultam together with pharmaceutically acceptable excipients in the form of a liquid gel, rinse solution or as an emulsion. These compositions according to the invention may be used either by themselves or in conjunction with surgery to combat the infection.

One particularly useful aspect is the impregnation of a gauze strip with a taurolidine and/or taurultam-containing emulsion which can be applied to the affected area by the dentist or orthodontist.

A taurolidine and/or taurultam containing gel is particular convenient for prophylactic use. A tube of the gel can be given to the patient who will then apply it to the affected area, as required, for example up to 6 times a day, depending on the extent of surgery and the strength of the gel.

Typically, an orally acceptable composition according to the present invention will comprise 0.5 to 5% taurolidine by weight, preferably 1 to 3% by weight, or 0.75 to 7.5% by weight of taurultam, preferably 1.5 to 4.5%.

The invention further provides a method of combatting severe dental infections (as defined herein),

- 8 -

said method comprising administering an orally acceptable taurolidine and/or taurultam-containing composition to the affected area of the patient.

According to a particular feature of the invention we provide the use of taurolidine and/or taurultam for combatting severe dental infections such as parodontitis, dental gangrene or abscesses and for the manufacture of dental compositions for such treatment.

The liquid compositions of the invention are particularly adapted for combatting dentoalveolar infections, such as gangrene or abscesses, for example by introduction via a syringe into tooth canals or application at or near the site of infection for delayed release. Such liquid compositions include emulsions, as indicated hereinafter, which may be applied via an impregnated gauze strip overlying the infected area, as well as rinse solution which can be used in the treatment of gangrene, abscesses and perikornitis and liquid dental gels which can be introduced via a syringe in the treatment of gangrene, apical astitis and root canal treatment.

Taurolidine has been tested for a number of orodental indications against therapy using conventional antibacterials. It could be seen that all target variables fell significantly more quickly under taurolidine medication than under conventional therapy. The total treatment time in the standard group was about 40% longer than in the taurolidine group. Moreover significantly less antibiotics and analgetics were required under taurolidine medication than under standard therapy. In contrast to most of the conventional preparations, which implicate a lot of side effects as irritation of smell and taste, discoloring of teeth and fillings, allergic reactions and histotoxicity with consecutive necroses, taurolidine only shows slight pain for some minutes after application during the acute period of inflammation.

- 9 -

The following study clearly demonstrates that treatment of severe dental infections using taurolidine compositions results in a marked decrease in the length of treatment time.

Comparison of Taurolidine and Conventional Treatments for Dentoalveolar Infections

Material and Methods

The in-vivo tests were carried out at the Clinic for Maxillofacial Surgery, Munich University between 1989 and 1992. In accordance with modern biometric principles the study was planned as a controlled clinical trial, i.e. it was conducted according to a prospective, protective, randomized, monocentre and simple blind design.

Indications

The following 6 indications examined were selected specifically on the basis of their incidence and clinical relevance.

- Alveolitis sicca dolorosa
- Gangrene
- Parodontitis marginalis
- Pericoronitis
- Abscess
- Infection prophylaxis

Test preparations

The test substances investigated were 4 different galenic presentation forms of the active component taurolidine and 4 conventional finished pharmaceuticals.

- Taurolidine® irrigation fluid 3% (Geistlich, Wolhusen/ Switzerland) (1 ml cont.: 30 mg taurolidine, 50 mg PVP 17)

- 10 -

- Taurolidine<sup>R</sup> liquid gel 3% (Geistlich, Wolhusen/Switzerland) (1 g cont.: 30 mg taurolidine, hydroxycellulose)
- Taurolidine<sup>R</sup> dental emulsion 3% (Geistlich, Wolhusen/ Switzerland) (1 g cont.: 30 mg taurolidine, fatty acid triglyceride, lecithin)
- Taurolidine<sup>R</sup> dental gel 2% (Geistlich, Wolhusen/Switzerland) (1 g cont.: 20 mg taurolidine, hydroxycellulose, gluside, polysorbates)
- AUREOMYCIN<sup>R</sup> ointment 3% (Cynamid-Novalis, Wolfratschausen/FRG) (1 g cont.: 30 mg chlorotetracycline, vaseline-anhydrous lanolin)
- DONTISOLON<sup>R</sup> ointment Type M (Hoechst, Frankfurt Germany) (1 g cont.: 5 mg prednisolone, 2 mg neomycin HCL, 3 mg aminoquinuride 2HCl 3.5 H<sub>2</sub>O, excipients)
- CHKM<sup>R</sup> solution (Haupt, Wurzburg/Germany) (1 ml cont.: 295 mg p-chlorophenol, 767 mg camphor, 18 mg menthol)
- CHLORHEXAMED<sup>R</sup> dental gel 1% (Blend-a-med, Mainz/Germany) (1 g cont.: 10 mg chlorhexidine digluconate, excipients).

#### Therapy regimens

For each of the 6 indications investigated an exact therapeutic procedure was fixed. The surgical management was carried out according to the individual situation in the usual manner. Tables 1 and 2 show the antimicrobial therapy regimens defined for patient groups A (Taurolidine group) and B (Standard group). It is evident, that the only difference, with the same

- 11 -

quantity of substance applied in the same form, was the choice of preparation.

Table 1

## THERAPY REGIMENT PATIENT GROUP A

DIAGNOSIS	PREPARATION	QUANTITY	APPLICATION
ALVEOLITIS	T-Irrigation fluid 3%	3.0 ml	Irrigation
	T-Dental emulsion 3%	0.5-1.0 g	Strip-charging or local application
GANGRENE	T-Irrigation fluid 3%	3.0 ml	Irrigation
	T-Liquid gel 3%	0.05-0.1 g	Canal instillation
PARODONTITIS	T-Liquid gel 3%	0.1-0.2 g	Sulcus instillation
	T-Dental emulsion 3%	0.5-1.0 g	Sulcus instillation
PERICORONITIS	T-Irrigation fluid 3%	3.0 ml	Irrigation
	T-Dental emulsion 3%	0.5-1.0 g	Strip-charging or local application
ABCESS	T-Irrigation fluid 3%	3.0 ml	Irrigation
	T-Dental emulsion 3%	0.5-1.0 g	Strip-charging or local application
INFECTION PROPHYLAXIS	T-Dental gel 2%	1.0-2.0 g	Local application

T represents "Taurolin" in the Table above.

- 12 -

Table 2

## THERAPY REGIMEN PATIENT GROUP B

DIAGNOSIS	PREPARATION	QUANTITY	APPLICATION
ALVEOLITIS	NaCl Solution 0.9%	3.0 ml	Irrigation
	AUREOMYCIN Ointment 3% 0.5-1.0 g		Strip-charging
GANGRENE	H <sub>2</sub> O <sub>2</sub> Solution 3%	3.0 ml	Irrigation
	CHKM Solution	0.05-0.1 g	Canal instillation
PARODONTITIS	DONTISOLON Ointment M	0.1-0.2 g	Sulcus instillation
PERICORONITIS	NaCl Solution 0.9%	3.0 ml	Irrigation
	AUREOMYCIN Ointment 3% 0.5-1.0 g		Strip-charging
ABSCESS	NaCl Solution 0.9%	3.0 ml	Irrigation
	AUREOMYCIN Ointment 3% 0.5-1.0 g		Strip-charging
INFECTION	CHLORHEXAMED	1.0-2.0 g	Local application
PROPHYLAXIS	Dental gel 1%		

Investigated parameters and randomization

For critical examination of the effectiveness of the different pharmaceuticals concerning therapeutic success and total treatment time clinical parameters reflecting the progress of recovery were controlled and documented at every session. The following 6 target variables were defined and evaluated by a uniform scale (0 = none to 4 = very strong):

- Pain
- Swelling
- Secretion

localisation of the lesions corresponded to the experiences in dental medicine. Alveolitis sicca dolorosa (67.5%) and pericoronitis (90.5%) mostly occurred in the lateral part of the mandible, while the other indications were well distributed between upper and lower jaw.

Both antibiotics as well as analgetics had been administered more often in the standard group than in the taurolidine group. The differences were statistically significant ( $p = 0.007$  resp.  $p = 0.01$ ).

#### Progress of therapy

As is evident from Table 3 all target variables fell more quicker under taurolidine medication than under conventional therapy. For example it can be seen that those patients who were treated with taurolidine were pain-free an average of 2 days earlier than those under conventional treatment. All results were statistically highly significant in Wilcoxon-Mann-Whitney U-test ( $p < 0.0001$ ).

Table 3

TARGET VARIABLES	PAIN		SWELLING		SECRETION		PRESSURE PAIN		PERCUSSION	
	TAUR	STAN	TAUR	STAN	TAUR	STAN	TAUR	STAN	TAUR	STAN
n (total)	600	600	600	600	600	600	600	600	600	600
Minimum	1	1	1	1	1	1	1	1	1	1
Maximum	14	21	14	24	15	18	15	18	13	17
Mean	5.3	7.3	4.5	6.2	3.9	5.0	5.3	7.3	1.9	2.4
STD DEV	2.3	3.0	2.5	3.5	2.5	3.5	2.3	2.9	1.9	2.8
P (U-Test)	< 0.0001		< 0.0001		< 0.0001		< 0.0001		< 0.0001	

- 13 -

- Pressure pain
- Repercussion
- Remission

The score-level 5 (total) was given at the moment of complete remission and describes consequently the final point of treatment.

As modifying variables were recorded:

Age, sex, optional analgetic and antibiotic application as well as the site of lesion.

200 cases were treated in each indication group, the total number amounted to 1,200. The distribution into the two therapy regimens was realised by random sampling. Statistical evaluations were made by means of testing methods described in customary literature.

### Results

The homogeneity tests carried out showed no statistically differences whatever ( $p > 0.05$ ), that is the comparability of the two patient groups was guaranteed.

### Characterisation of patients

The patients ranged between 1 and 89 years of age, with a mean of 38.7 years (Standard deviation STD DEV =  $\pm 16.3$ ). As was expected, stratification according to the indications showed moderate fluctuation (Pericoronitis with a mean of 29.4 years to parodontitis with a mean of 43.5 years).

The distribution of the sexes showed men (57.3%) to be in a small majority and this trend was the same across all indication groups. At first this fact seems to be astonishing, but it is in accordance with the total sex distribution in our clinic patients, which exhibits 54.5% males vs. 45.5% females (1991). The

-15-

Total treatment time

Tables 4 and 5 show the course of the remission for the two therapy regimens. A superior effectiveness of taurolidine to the standard therapy was demonstrable for all 6 indications corresponding to a clinical relevant more rapid recovery ( $p < 0.0001$ ). Furthermore it is striking that the standard deviations in the taurolidine group were generally smaller than the comparable values in the standard group. This is also a fact that allows the dentist a better estimation of the required treatment time. Any influence of the investigated modifying variables as age, sex, localisation of the lesion and optional antibiotic or analgetic administration on the process of recovery as well as on total treatment time could not be shown neither in the taurolidine nor in the standard group.

Table 4

DIAGNOSIS	ALVEOLITIS		GANGRENE		PARODONTITIS	
TIME (days)	TAUR.	STANDARD	TAUR.	STANDARD	TAUR.	STANDARD
n (total)	100	100	100	100	100	100
Minimum	3	3	2	3	2	3
Maximum	15	18	10	24	14	15
Mean	5.6	8.2	5.0	7.7	5.1	6.4
STD DEV	2.5	3.2	1.8	3.7	2.1	2.2
P (U-Test)	< 0.0001		< 0.0001		< 0.0001	

-16-

Table 5

DIAGNOSIS	PERICORONITIS		ABSCESS		INFECT. PROPHYLAXIS	
TIME (days)	TAUR.	STANDARD	TAUR.	STANDARD	TAUR.	STANDARD
n (total)	100	100	100	100	100	100
Minimum	2	3	2	3	3	5
Maximum	12	18	13	16	13	16
Mean	5.1	7.3	5.5	7.7	7.5	10.0
STD DEV	1.9	2.9	2.1	2.8	1.8	2.3
P (U-Test)	< 0.0001		< 0.0001		< 0.0001	

The invention is further illustrated by the following, non-limiting Examples.

- 17 -

Example 1

3% Taurolidine Dental Emulsion

Preparation of 4.0 kg

Composition:	% (by weight)
--------------	---------------

A	Egg lecithin	5.00
	Distilled water	46.00
B	Distilled water	24.00
	Natrosol 250 HHR	0.50
C	Taurolidine	1.00
D	Glycerylmonostearate	5.00
	Soya oil	10.00
E	Oleum Menthae Supramint BP	0.30
F	Taurolidine (micronised)	2.00
	Distilled water	<u>6.20</u>
		<u>100.00</u>

Preparation:

- A Dissolve with stirring;
- B disperse completely with stirring;
- C add to A and dissolve;
- B add to A/C and homogenise. Heat to 70°C;
- D mix with heating to 70°C;

- 18 -

add the fatty phase to the aqueous phase in an emulsifying device and emulsify;  
cool with stirring to 25°C;

E add and mix in;

F disperse and add to the product;  
homogenise again.

Example 2

3% Taurolidine Dental Emulsion

	Composition:	% (by weight)
A	Egg lecithin	5.00
	Distilled water	43.00
B	Distilled water	22.00
	Kollidon 17 PF	5.00
	Natrosol 250 HHR	0.50
C	Taurolidine	1.00
D	Glycerylmonostearate	5.00
	Soya oil	10.00
E	Oleum Menthae Supramint BP	0.30
F	Taurolidine (micronised)	2.00
	Distilled water	<u>6.20</u>
		<u>100.00</u>

- 19 -

### Preparation:

- A Dissolve with stirring;
- B disperse completely with stirring;
- C add to A and dissolve;
- B add to A/C and homogenise. Heat to 70°C;
- D mix with heating to 70°C;  
add the fatty phase to the aqueous phase in an emulsifying device and emulsify;  
cool with stirring to 25°C;
- E add and mix in;
- F disperse and add to the product;  
homogenise again.

### Example 3

### 3% Taurolidine Dental Emulsion

Composition:		% (by weight)
A	Egg lecithin	5.00
	Distilled water	43.00
B	Distilled water	22.00
	PEG 4000	5.00
	Natrosol 250 HHR	0.50
C	Taurolidine	1.00
D	Glycerylmonostearate	5.00

- 20 -

	Soya oil	10.00
E	Oleum Menthae Supramint BP	0.30
F	Taurolidine (micronised)	2.00
	Distilled water	<u>6.20</u>
		<u>100.00</u>

**Preparation:**

- A Dissolve with stirring;
- B disperse completely with stirring;
- C add to A and dissolve;
- B add to A/C and homogenise. Heat to 70°C;
- D mix with heating to 70°C;  
add the fatty phase to the aqueous phase in an  
emulsifying device and emulsify;  
cool with stirring to 25°C;
- E add and mix in;
- F disperse and add to the product;  
homogenise again.

**Example 4**

**3% Taurolidine Dental Emulsion**

Composition: % (by weight)

A	Egg lecithin	5.00
---	--------------	------

- 21 -

	Distilled water	43.00
B	Distilled water	22.00
	PEG 20,000 (and higher up to 100,000)	5.00
	Natrosol 250 HHR	0.50
C	Taurolidine	1.00
D	Glycerylmonostearate	5.00
	Soya oil	10.00
E	Oleum Menthae Supramint BP	0.30
F	Taurolidine (micronised)	2.00
	Distilled water	<u>6.20</u>
		<u>100.00</u>

**Preparation:**

- A Dissolve with stirring;
- B disperse completely with stirring;
- C add to A and dissolve;
- B add to A/C and homogenise. Heat to 70°C;
- D mix with heating to 70°C;  
add the fatty phase to the aqueous phase in an  
emulsifying device and emulsify;  
cool with stirring to 25°C;
- E add and mix in;

- 22 -

F disperse and add to the product;  
homogenise again.

Example 5

3% Taurolidine Dental Emulsion

	Composition:	% (by weight)
A	Egg lecithin	5.00
	Distilled water	43.00
B	Distilled water	24.00
	Natrosol 250 HHR	0.50
C	Taurultam	4.5
	Distilled water	4.7
D	Glycerylmonostearate	8.00
	Soya oil	10.00
E	Oleum Menthae Supramint BP	<u>0.30</u>
		<u>100.00</u>

**Preparation:**

A Dissolve with stirring;

B completely disperse with stirring;

C dissolve and add to A;

B add to A/C and homogenise. Heat to 70°C;

- 23 -

D mix with heating to 70°C;  
add the fatty phase to the aqueous phase in an  
emulsifying device and emulsify;  
cool with stirring to 25°C;

E add and mix in.

Example 6

Taurolidine Liquid Dental-Gel 2%

Composition: % (by weight)

Taurolidine	2.00
Lidocaine HCl	2.00
Edible gelatin S 08.080	0.30
Natrosol 250 HHR	0.75
Carbopol 941	0.75
Distilled water	91.15
Saccharine solution 10%	0.40
Tween 20	0.80
Tween 80	1.60
Oleum Menthae Supramint BP	0.25

KOH 50%ig pH 7.2 pH 7.20

Preparation:

Dissolve taurolidine, lidocaine and edible gelatin in water with warming;  
cool to ambient temperature;  
add the natrosol and homogenise;  
add the carbopol and disperse;  
allow to fully swell with stirring;  
add saccharine solution;  
mix the Tweens and Oleum Menthae and add;  
adjust the pH with KOH.

- 24 -

Claims

1. Use of taurolidine and/or taurultam in the preparation of an orally acceptable medicament for combatting severe dental infection or dental infection following dental surgery.
2. Use as claimed in claim 1, wherein said severe dental infection is gangrene, parodontitis or dental abscesses.
3. Use as claimed in either of claims 1 and 2, wherein said medicament is in the form of a gel, emulsion, liquid gel or rinse solution.
4. An orally acceptable composition in the form of a liquid gel, rinse solution or emulsion, said composition comprising taurolidine and/or taurultam together with a pharmaceutically acceptable excipient.
5. An orally acceptable gauze strip impregnated with an emulsion as claimed in claim 4.
6. A method of combatting severe dental infection or dental infection following dental surgery, said method comprising administering an orally acceptable composition comprising taurolidine and/or taurultam to the affected area of the patient.
7. Use of taurolidine and/or taurultam to combat severe dental infection or dental infection following dental surgery.

## INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 93/01607

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)<sup>6</sup>

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl. 5 A61K31/54

## II. FIELDS SEARCHED

Minimum Documentation Searched<sup>7</sup>

Classification System	Classification Symbols
Int.Cl. 5	A61K

Documentation Searched other than Minimum Documentation  
to the Extent that such Documents are Included in the Fields Searched<sup>8</sup>III. DOCUMENTS CONSIDERED TO BE RELEVANT<sup>9</sup>

Category <sup>10</sup>	Citation of Document, <sup>11</sup> with indication, where appropriate, of the relevant passages <sup>12</sup>	Relevant to Claim No. <sup>13</sup>
X	GB,A,1 557 163 (ED. GEISTLICH SÖHNE A.G.) 5 December 1979 cited in the application see the whole document ----	1-4,6,7
Y	DE,A,2 618 666 (GABA AG) 18 November 1976 see the whole document ----	1-7
X	ED. BRÜCKNER 'Taurolin-ein neues Konzept zur antimikrobiellen Chemotherapie chirurgischer Infektion; Chapter 43' 1985 cited in the application	1-4,6,7
Y	G.H. NENTWIG ET AL.: 'Erste klinische Erfahrungen mit Taurolin-Feingranulat in der zahnärztlichen Chirurgie' see page 287 - page 289 ----	5
X	ED. BRÜCKNER 'Taurolin-ein neues Konzept zur antimikrobiellen Chemotherapie chirurgischer Infektion; Chapter 43' 1985 cited in the application G.H. NENTWIG ET AL.: 'Erste klinische Erfahrungen mit Taurolin-Feingranulat in der zahnärztlichen Chirurgie' see page 287 - page 289 ----	1,2,6,7
Y	-----	3-5
	-----	-/--

<sup>10</sup> Special categories of cited documents :<sup>10</sup>

- <sup>A</sup> document defining the general state of the art which is not considered to be of particular relevance
- <sup>E</sup> earlier document but published on or after the international filing date
- <sup>L</sup> document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- <sup>O</sup> document referring to an oral disclosure, use, exhibition or other means
- <sup>P</sup> document published prior to the international filing date but later than the priority date claimed

- <sup>T</sup> later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- <sup>X</sup> document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step
- <sup>Y</sup> document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- <sup>&</sup> document member of the same patent family

## IV. CERTIFICATION

Date of the Actual Completion of the International Search <b>29 SEPTEMBER 1993</b>	Date of Mailing of this International Search Report <b>12.10.93</b>
International Searching Authority <b>EUROPEAN PATENT OFFICE</b>	Signature of Authorized Officer <b>KRAUTBAUER B.</b>

## INTERNATIONAL SEARCH REPORT

PCT/GB 93/01607

International Application No

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)		
Category	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
X	FORTSCHR. KIEFER GESICHTSCHIR. vol. 30, 1985, pages 35 - 37 G.H. NENTWIG ET AL. 'Zur Behandlung postchirurgischer Knocheninfektionen' see the whole document ---	1,2,6,7
Y		1-7
X	CLIN PREV DENT vol. 13, no. 2, 1991, pages 13 - 22 REYNOLDS ET AL. 'Taurolin as an oral rinse I. Antimicrobial effects in vitro and in vivo.' see the whole document ---	4
Y		1-3,5-7
Y	EP,A,0 139 534 (ED. GEISTLICH SÖHNE A.G.) 2 May 1985 see the whole document ---	2
P,X	ARZNEIMITTELFORSCHUNG vol. 42, no. 9, September 1992, pages 1157 - 1159 M. ZIMMERMANN ET AL. 'In vitro activity of taurolidine, chlorophenol-camphor-menthol and chlorhexidine against oral pathogenic microorganisms' see the whole document ---	1,6,7
Y		2-5
P,X	INT. J. CLIN. PHARMACOL. THER. TOXICOL. vol. 31, no. 3, March 1993, pages 130 - 136 M. ZIMMERMANN ET AL. 'The antimicrobial actions of taurolin and other preparations on the pathogenic spectrum in dentoalveolar infections' see the whole document ---	1-4,6,7
Y		5
P,X	EP,A,0 521 225 (HAWE-NEOS DENTAL DR. H. V. WEISSENFLUH AG) 7 January 1993 see the whole document -----	1-4,6,7

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/GB93/01607

**Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
**REMARK: Although claim 6 is directed to a method of treatment of the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.**
2.  Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

**Remark on Protest**

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT  
ON INTERNATIONAL PATENT APPLICATION NO.

GB 9301607  
SA 77548

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

29/09/93

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-1557163	05-12-79	AU-B-	508421	20-03-80
		AU-A-	1516776	05-01-78
		BE-A-	843359	24-12-76
		CA-A-	1066622	20-11-79
		DE-A, C	2628265	20-01-77
		FR-A, B	2316954	04-02-77
		US-A-	4096241	20-06-78
DE-A-2618666	18-11-76	CH-A-	600878	30-06-78
		CA-A-	1100045	28-04-81
		FR-A, B	2309231	26-11-76
		GB-A-	1555106	07-11-79
		GB-A-	1555107	07-11-79
		GB-A-	1555108	07-11-79
		JP-C-	1348723	28-11-86
		JP-A-	51133435	19-11-76
		JP-B-	61008041	11-03-86
		NL-A-	7604527	01-11-76
		SE-B-	435677	15-10-84
		US-A-	4308253	29-12-81
		US-A-	4219541	26-08-80
EP-A-0139534	02-05-85	AU-A-	3457484	09-05-85
		BE-A-	900855	15-02-85
		CH-A-	660969	30-06-87
		DE-A-	3438470	30-05-85
		DE-A-	3486150	01-07-93
		JP-A-	60105617	11-06-85
		US-A-	4604391	05-08-86
EP-A-0521225	07-01-93	None		